

REMARKS

Claims 1-10, 12-27, 40-48 and 52 were pending in the application. Of those, claims 18-27 and 52 were withdrawn from consideration. Claims 1-10, 12-17 and 40-48 were examined and rejected under various grounds (see below).

The following claims are being canceled without prejudice or disclaimer, either due to their incorporation into parent claims or to focus on other embodiments: 2-5, 14, 16, 17 and 41-46.

Withdrawn claims 19 and 52 are also being canceled

The following active claims are being amended: 1, 6-8, 12, 13, 47 and 48

The following withdrawn claims are being amended in line with the amendment of the above active claims: 18, 22, 23, 25 and 26

As indicated in the specification (Table 1B, page 20), there appears to be an inverse correlation between SIRS and gram positive infection. Accordingly, dependent claims 8-13 and 40, 47 and 48 follow two independent lines, (*i.e.*, claim 8-13 focus on the alleles associated with SIRS, sepsis and septic shock and the claims 40, 47 and 48 focus on alleles associated with gram positive infection.

As a result of the above cancelations, claims 1, 6-10, 12, 13, 15, 18, 20-27, 40, 47 and 48 are pending. Of these claims 18, 20-27 are withdrawn. The active claims under examination are 1, 6-10, 12, 13, 15, 40, 47 and 48.

None of the amendments introduces new matter and entry of the amended claims is respectfully requested, as is allowance of these claims..

I. Priority

The Office reminds Applicants of the need to refer specifically to the prior-filed application in compliance with 37 CFR 1.78(a) in the first sentences of the specification following the title or in an application data sheet (ADS).

Applicants are filing an ADS with this Response and therefore comply with the statute and rules.

II. Defective Oath/Declaration

The oath/declaration was allegedly defective as not identifying the citizenship of each inventor because of the erroneous listing of "British Columbia" as citizenship rather than merely as the province of residence, where "Canada" was the intended citizenship.

In response, a substitute Declaration and an ADS are submitted herewith.

III. Information Disclosure Statement (IDS)

The IDS submitted on 8/31/2006 has been considered by the examiner, although the Action notes that the IDS filed 6/25/2008 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each NPL publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. This allegedly defective IDS has been placed in the application file, but the information referred to therein was not considered.

The Action notes that the reference of Sutherland on the IDS of 6/25/2008 has been considered by the examiner, as the art is used in the 35 USC 112 rejection recited below. As such, Applicant is not required to submit a copy

Applicants' Response

Further to a discussion with the Examiner, Applicants earlier submitted (on 4/29/2010) a listing of two references on form SB08a and copies of these two references.

IV. Objections to the Disclosure

Specification

The disclosure was objected to because on p. 38 line 14 of the specification, a reference is referred to as "anonymous." The Action requires a correction to be made to clearly describe the article with which the specification is referring to by the appropriate author's name.

Applicants' Response

This paper, *Crit Care Med.* 1992 Jun; 20:864-74. specifically state "no authors listed." The publication is noted as being from the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: "Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis."

Applicants have presented all the information that is available to them.

V. Claim Objections

A. Claims 1-10, 12-17, and 40-48

These claims were objected to because of the following informalities:

- The phrase “**increased at risk**” in claim 1 line 2 is grammatically incorrect and should be amended to “**increased risk of**”.
- The **comma after “developing”** in line 2 of claim 1 should be removed.
- Claims 2-10, 12-15, and 40-48 are objected to as depending from this objected claim.

Applicants have corrected these errors in those claims which remain.

B. Claims 14 and 17

These claims are objected to lacks proper punctuation separating each item listed in the claim. Improper inclusion of both a semicolons and a comma in places is improper, as is jumping from one form of punctuation (comma) and another (semicolon) in a list of embodiments.

Applicants note that these two claims have been canceled, rendering the objections moot.

C. Claims 13 and 48

These claims were found to be grammatically incorrect, because the phrase “defined as homozygosity” should be “defined as homozygous”.

Although Applicants disagree with the Office’s grammatical interpretation, they have amended these claims to recite “homozygous.”

D. Claim 16(b)

The Examiner noted an extra space before a semicolon in the last sentence. Because this claim is being canceled, this objection is moot.

VI. REJECTION UNDER - 35 U.S.C. § 101

Claims 1-4, 7-10,12-17,40-42, and 45-48 were rejected because the claimed invention is allegedly directed to non-statutory subject matter.

The Action states that in claims drawn to determining a genotype, this determining step could be a mental step, such as (in claims 7 and 45) the embodiment “reading sequence data” because this would encompass determining a genotype by looking at a computer database. Therefore the methods as claimed do not meet the machine or physical transformation required by the Federal Circuit as discussed in *In re Bilski* (88 U.S.P.Q.2d 1385). The Action states that these rejections can be overcome by amending the claims to include a step of obtaining a sample.

Applicants' Response

Claim 7 has been amended to remove option (i) "reading sequence data" whereas claim 45 has been canceled.

Claim 1 has been amended to recite specifically that the determining is performed "in a nucleic acid sample from a subject" (imported from claim 5, now canceled, and which was free of this rejection). Applicants elect not to include an "obtaining" step in claim 1 for reasons that do not require discussion at this point; note that such a step is added in dependent claim 6.

In their present form, the rejected claims cannot be interpreted as mere "mental steps", so this rejection should be withdrawn.

VII. Rejections Under - 35 USC § 112/2nd Paragraph (Indefiniteness)

Claims 1-10, 12-15, and 40-48 were rejected as being indefinite for a number of reasons listed below, as a result of which a person of ordinary skill in the art allegedly would not be reasonably apprised of the scope of the invention claimed.

The terms "**enhanced recovery**" and "**enhanced ability**" in claim 1 are a relative terms which render the claim indefinite. The term "**enhanced**" is allegedly not defined by the claim nor does the specification provide a standard for ascertaining the requisite degree. Specifically the Office asserts that it is not clear the degree of recovery which is required to be "enhanced". For example it is not clear if recovery at a normal rate would be considered "**enhanced**". As such the metes and bounds of the claim are not clear.

The term "**poor**" in claim 8 is a relative term which renders the claim indefinite as allegedly, the term is not defined by the claim nor does the specification does not provide a standard for ascertaining the requisite degree.

Specifically it is not clear which outcomes would be considered **poor** outcomes. For example, according to the Office, having a treatable disease condition would be considered a "poor outcome" compared to not having a disease, but having an untreatable disease would also be a "poor outcome." As such, the degree of a "poor" outcome which must be observed to be considered within the metes and bounds of the claims is not clear.

The term "**critically ill**" in claims 9 and 12 is a relative term which allegedly renders the claim indefinite as the term allegedly is not defined by the claim, nor does the specification provide a standard for ascertaining the requisite degree. Specifically it is not clear how ill a subject must be .

For example it is unclear if the term would encompass any level of illness or if the claim requires **some requisite degree of illness**.

The terms “**severe**” and “**less severe**” in claims 9 and 12 are relative terms which allegedly render the claim indefinite. The terms “severe” and “less severe” are allegedly not defined by the claim, and the specification does not provide a standard for ascertaining the requisite degree. Specifically if it not clear **which CV or respiratory dysfunctions** would be indicative of severe or less severe dysfunction. For example a normal level of CV dysfunction in a patient with sepsis would be more severe than a patient without sepsis but at the same time it would be less severe than a patient with full septic shock. Therefore the same condition could be considered both severe and less severe. As such the metes and bounds of the claims are not clear.

Applicants’ Response

Applicants disagree with the Office’s assessment of all these terms. The use of these terms would be understood by a person of skill in this art. The application sets out clear criteria for assessing patient outcome. For example, at pages 22-25, the specification describes the systems of APACHE II scoring and Brussels scoring as methods for determining a patient’s outcome or prognosis. Accordingly, Applicant submits that all these terms which the Office considers to indefinite are, in fact definite. Claims have been allowed in similar applications by the same applicants inventors that use precisely such terminology (e.g., U.S. Application 10/515,493 issued on 10/26/2010 as U.S. Pat. 7,820,376 (emphasis added))¹

¹ Claim 1: A method for determining a prognosis for a human subject having, or at risk of developing, an inflammatory condition, the method comprising determining a genotype of said human subject at a polymorphic sites in the subject’s protein C gene at position 2418 of SEQ ID NO:1, wherein said genotype is indicative of the subject’s **ability to recover** from the inflammatory condition which is SIRS, sepsis or septic shock, wherein the relationship between the nucleotide at said position 2418, the inflammatory condition and the prognosis is as follows:

- (a) for SIRS, sepsis or septic shock:
 - (i) ...2418 AA homozygosity...is prognostic of a **decreased ability to recover**; and
 - (ii) ... 2418 GG homozygosity...is prognostic of an **increased ability to recover**; and
- (b) for septic SIRS:
 - ...2418AG heterozygosity...is prognostic of an **increased ability to recover compared to that of 2418 AA homozygosity and a decreased ability to recover compared to that of 2418 GG homozygosity**

Claim 11. The method of claim 1, wherein the subject is **critically ill**, and has a genotype prognostic of **decreased ability to recover** from the inflammatory condition and from severe cardiovascular or respiratory dysfunction ...

Claim 14. The method of claim 1, wherein the subject is **critically ill**, and has a genotype prognostic of **increased ability to recover** from the inflammatory condition and from mild cardiovascular or respiratory dysfunction...

In view of the foregoing, Applicants therefore contend that it would be proper to withdraw these grounds for rejection.

VIII. REJECTIONS UNDER - 35 USC § 112, FIRST PARAGRAPH (Enablement)

Claims 1-10,12-17, and 40-48 were rejected because the specification allegedly did not enable the scope of the claims.

The Office admits that the disclosure is enabling for

- (A) method for determining an increased risk of developing gram positive septic infection by determining the genotype at position 201 of SEQ ID NO: 1 in a nucleic acid sample obtained from a human subject, where AA genotype indicates that the subject has an increased risk of developing gram positive septic infection compared to patients who have an AT or a TT genotype at position 201 of SEQ ID NO:1.
- (B) A method for determining a decrease survival in a human gram positive sepsis by determining in a nucleic acid sample obtained from a human subject who has systemic inflammatory response syndrome (SIRS), the genotype at position 201 of SEQ ID NO:1, wherein the presence of AT or TT indicates that a prognosis of decreased survival compared to a patient who has an AA genotype.

In contrast, the Office contends that there is no reasonable enablement for determining prognosis in any subject (*i.e.*, other than human) of enhanced recovery from **any** inflammatory condition or increased risk of developing any inflammatory condition by determining a genotype at one or more polymorphic sites in the toll-like receptor 2 (TLR-2) gene. The enablement rejection relates to the lack of predictability in associating any position of TLR2 with any inflammatory disease. The Action states that the prior art provides some associations of specific SNP positions in TLR2 with specific inflammatory conditions (referring to the §102(b) rejections below. However, the prior art does not provide enabling support for the breadth of the examined claims. The Office notes that for compact prosecution, the scope of enablement is specific to the particular SNP and particular associations provided by the specification. As a “summary statement”, the Action indicates that neither the art nor the specification provide a predictable correlation between any SNP position in the TLR2 gene and any “general” inflammatory condition.

Applicants' Response

For the sake of brevity Applicants will not go through the entire *Wands* analysis in their response, particularly because they believe that the present amendments, particularly to claim 1, deal with all the issues raised and results in a set of claims all of which fall within the scope of what the Office admits to being enabled by Applicants' specification in view of the state of the art.

To summarize, the key amendments to claim 1 are the following, and their "deviation" from the lines drawn by the Office are discussed afterwards in more detail.

- Claims are limited to human subjects.
- Claims limited to polymorphism at a single position in the TLR2 gene, namely, the SNP at position 201 in SEQ ID NO:1. There is no reference to, or inclusion of, additional SNPs in linkage disequilibrium (LD) with position 201.
- The prognostic method is now limited to the following conditions (a) **gram positive infection**, and (b) a narrow array of inflammatory conditions, namely **SIRS, sepsis and septic shock**.
- The genotypes (protective and risk) differ depending on whether the indication is SIRS, sepsis and septic shock on the one hand or a gram positive infection on the other.

The three inflammatory conditions are defined as follows in the specification, at page 21, lines 20-31:

A "systemic inflammatory response syndrome" or (SIRS) is defined as including both septic (*i.e.* sepsis or septic shock) and non-septic systemic inflammatory response (*i.e.* post operative). "SIRS" is further defined according to ACCP (American College of Chest Physicians) guidelines as the presence of two or more of A) temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, B) heart rate >90 beats per minute, C) respiratory rate >20 breaths per minute, and D) white blood cell count $>12,000$ per mm^3 or $<4,000$ mm^3 . In the following description, the presence of two, three, or four of the "SIRS" criteria were scored each day over the 28 day observation period.

"Sepsis" is defined as the presence of at least two "SIRS" criteria and known or suspected source of infection. Septic shock was defined as sepsis plus one new organ failure by Brussels criteria plus need for vasopressor medication.

Applicants submit herewith a document by Bone *et al.* (hereinafter, "**Bone**") , "Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis," THE ACCP/SCCM CONSENSUS CONFERENCE COMMITTEE: Chest (1992) 101:1644-55). This publication was the result of the work of Consensus Conference Committee of the American College of Chest Physicians/Society of Critical Care Medicine on sepsis and organ failure. At page 45-46, **Bone** defines "sepsis" as being the same as the definition provided at page 21 of the specification.

Bone defines “severe sepsis” and “septic shock” in a way that those skilled in the art would consider them encompassed by SIRS. For example:

- (i) “severe sepsis” is sepsis with organ dysfunction, hypoperfusion, or hypotension and
- (ii) “septic shock” is sepsis induced with hypotension despite adequate fluid resuscitation along with perfusion abnormalities).

It would appear that anyone with sepsis or suffering from septic shock suffers from SIRS as they would have to have at least two of the four SIRS criteria. Furthermore, in the exemplary section of the specification, for example, page 44, line 1 through page 49, line 26 and in Tables 5-8), the specification refers to (and provides data for) patient populations using the terms “SIRS” and “sepsis.”

Considering the foregoing, it would be proper to conclude that the specification provides the necessary support (also written descriptive support) together with the state of the art for the scope of amended claim 1 as regards the types of claimed inflammatory conditions. Applicants therefore request withdrawal of this ground of rejection.

Office’s Discussion of Statistical Significance of Applicants’ Results and the Sutherland *et al.* Reference

The Action states that “the specification provides no statistically significant correlation between the presence of any SNP, in particular the SNP at position 201, and improved prognosis of an inflammatory condition” and that

“statistically significant associations between a particular SNP and particular inflammatory conditions must be each tested individually and validated. There is no expectation of success for each such association as the art teaches that a structural difference in TLR2 is not sufficient to predict an association to an inflammatory condition.”

Reference is made to the Sutherland *et al. Crit Care Med* 2005, 33;638 (“Sutherland”) disclosure that the genotype of AA at position 201 of SEQ ID NO:1 was **not** associated with survival. The Office appears to have concluded from this that “the art teaches that although some correlations might be predictive, those as broad as the claims are not predictable.” Specifically

“even when a skilled artisan examines only one polymorphic position of TLR2, the associations of the genotypes and inflammatory conditions *can* (Applicants believe the Examiner meant “cannot”) be directly extrapolated to one another.”

The Office further alleges that

...even at position 201, the claims would encompass associations between three genotypes, AA, AT, and TT, and prognosis of recovery, or increased risk of developing an inflammatory condition. These associations must each be evaluated individually and the correlation of one association is not predictive of the correlation of any other association. In particular, as noted in the paragraph above, an association of AT or TT with survival does not provide guidance as to whether the genotype AA is associated with survival. Although the specification provides teaching of an association with decreased survival and AT or TT, the state of art (e.g., Sutherland *et al.*), teaches that there is no association between survival and the AA genotype.

Further on, the Action states:

Post-filing art teaches that even with the specific polymorphic position of 201 of SEQ ID NO:1 each association to inflammatory condition must be individually examined and validated. **Sutherland** (*Crit Care Med* 2005, 33;638) teaches that patients were used which had at least 2 of the 4 SIRS criteria and therefore were considered critically ill (p. 639 2nd col, 2nd para). **Sutherland** discloses that these patients were genotyped for polymorphisms in TLR2 (p. 639 2nd col, 3rd para) and detection of the same SNP region as the instant specification (-16933 T/A SNP) (p. 640 1st para). TLR2 -16933AA was associated with significant increased prevalence of sepsis on admission to the ICU (p <0.03, Figure 7) and specifically, with increased prevalence of Gram positive infections (p=0.04) (p. 641 1st col, last para - 2nd col, 1st para). **Sutherland** states that AA was not associated with increased prevalence of positive bacterial cultures or septic shock on admission to the ICU or with a significant difference in 28 day survival (p. 641 2nd col, 1st para). The association to prevalence of sepsis on admission to the ICU is still unclear in the art as it is not clear what defines whether a patient has sepsis. **Sutherland** teaches that the admitted patients all had at least 2 or the 4 SIRS criteria and indicates that sepsis was defined as the presence of two or more SIRS criteria plus the presence of a known or suspected infection during the 24 hour period (p 639 3rd col, 2nd para). Therefore it appears that having two or more SIRS criteria defines the whole population studied as having sepsis.

Sutherland states that septic shock was defined by sepsis plus significant hypotension based on systolic blood pressure or the need for vasopressors (p. 639 3rd col, 3rd para). AA was not associated with increased prevalence of positive bacterial cultures or septic shock on admission to the ICU or with a significant difference in 28 day survival (p. 641 2nd col, 1st para).

Applicants' Response

Sutherland was an after-filing publication (by the present inventors and one non-inventor colleague) and discussed the same polymorphism in TLR-2 in association with infection in critically ill patients. It appears that the Office concluded that the findings in Sutherland contradict the findings set out in the present application.

The studies in Sutherland were conducted by the present inventors on a smaller patient cohort than the cohort which was reported both in the patent application.

The effect of the SNP at position 201 reported in the present application in a larger patient study population was not observed in Sutherland. It is not clear why the larger patient cohort was

not reported in Sutherland, but the fact is that there was a statistically significant effect in SIRS patients in the larger patient cohort. The results of the larger study is a better representation of the prognostic significance of the polymorphism at this site of the TLR2 gene (SEQ ID NO:1)

Furthermore, it appears that the Office tended not to accept that a trend (i.e. a result that does not reaching “statistical significance” using a conventional criterion in a particular statistical test) (e.g., a $p < 0.05$ level in a given test) is predictive or of prognostic value.

Applicants contend that the present data demonstrating “trends” are not to be dismissed. It is incorrect to conclude, as the Office has, that these data are “not predictive.” Applicants direct the Examiner’s attention to a section of a basic statistics textbook² which teaches at pages 400-401 that the p-value serves as a measure of the strength of the justification for rejecting the null hypothesis, and should not be viewed as an absolute value as seems to be the Office’s position. For example, a lower p-value (e.g., $p = 0.024$) may justify a heightened sense of confidence for rejecting the null hypothesis; a somewhat higher p value (e.g., 0.064 or 0.066) may also justify rejecting the null hypothesis, albeit with somewhat less confidence. Such values are, nevertheless, a proper basis for confidence that a meaningful “trend” is shown by the data. If the Examiner would find it useful or more convincing, Applicants can provide a Rule 132 Declaration from a statistician to support their above points.

It must be kept in mind that the patent statute and case law nowhere require a strict “cutoff” value of statistical significance (such as $p < 0.05$ in a given test) to support a claimed invention, much like there is no requirement for clinical data to support operability of an invention.

IX. REJECTIONS UNDER - 35 USC § 112, 1st Paragraph (Written Description)

Claims 1-10, 12-17, and 40-48 were are rejected as failing to comply with the written description requirement. The claims encompass a correlation of prognosis in a subject of enhanced recovery from an inflammatory condition or increased risk of developing the inflammatory condition by detecting one or more polymorphic sites in the TLR-2 receptor in a subject. The claims are further drawn to determination of one or more polymorphic sites which includes position 201 of SEQ ID NO:1 or a polymorphic site in LD therewith. The claims are drawn to correlations of the

² Khazanie, R, *Elementary Statistics in a World of Applications* 3rd Ed., 1990, beginning at page 400, submitted herewith

homozygous T genotype at position 201 of SEQ ID NO:1, the T allele at position 201 of SEQ ID NO:1 and the A allele at position 201 of SEQ ID NO:1 in a subject. The claims are broadly drawn to any polymorphic position of TLR-2 in any subject with the “functionality” of an association to inflammatory condition. This includes a large number of potential positions in the TLR-2 gene (not only in humans, but in any other species). Therefore the claims encompass selecting a subject (human or non human) having one or more of an enormous and wide variety of allelic variants in the TLR-2 gene or allelic variants in LD with position 201 of SEQ ID NO:1; nucleic acids of such a large genus have not been adequately described by the specification. The specification only describes one polymorphic position (position 201 of SEQ ID NO:1) in terms of function. The application allegedly lacks any analysis regarding polymorphisms in LD with position 201, or any polymorphic site of TLR2 in any subject.

Applicants’ Response

As discussed above with respect to the enablement rejection, claim 1 is amended to limit the scope to :

- the polymorphic site at position 201 of SEQ ID NO:1,
- the subjects to humans,
- the prognostic method to the following conditions (a) gram positive infection, and (b) a narrow array of inflammatory conditions, namely SIRS, sepsis and septic shock.

This scope corresponds to that which is considered adequately described. Therefore, claim 1 and all claims dependent therefrom are believed to comply with the written description requirement. It would therefore be proper to withdraw this ground for rejection.

X. REJECTIONS UNDER § 102 (Anticipation)

Claims 1-2, 4-9, 14-15, 40, and 42-46 were rejected under 35 U.S.C. 102(b) as being anticipated by Lorenz *et al.*, (*Infec Immun.* 2000 68:6398 (hereinafter “**Lorenz**”) cited in Applicants’ earlier IDS. The Action notes further that these claims were also been rejected under 35 U.S.C. 112/1st paragraph as not fully described or fully enabled by the specification, and that this reference does not provide a basis for an adequate written description or enablement of the of the breadth of the rejected claims.

Applicants note that the following claims are free of this rejection - 3, 10, 12, 13, 16, 17, 41, 47 and 48.

A slightly modified version of the Office's claim-by-claim analysis follows with applicants comments following each.

Claim 1: **Lorenz** teaches detecting a TLR-2 genotype defined by a polymorphic site - using detection and sequencing of a site which comprises TLR2 Arg753Gln (p. 6399 1st col, 3rd full paragraph). The genotype is indicative of increased risk for staphylococcal septic shock, a type of inflammatory condition. Because this site is associated with staphylococcal septic shock it defines a risk genotype.

Applicants note that this position is different from the presently claimed position 201 of SEQ ID NO:1.

Claim 2: The position taught by **Lorenz** would have some degree of LD with position 201 of the same gene. Therefore the Lorenz SNP broadly encompasses a SNP in LD with position 201 of SEQ ID NO:1

Applicants note that this claim is canceled; the claims are no longer related to SNPs in LD with the SNP at 201.

Claim 4: **Lorenz** teaches determining the genotype of the TLR-2

Applicants note that this claim is canceled.

Claims 5-7: **Lorenz** discloses SNP determination on the nucleic acid of the sample by sequencing and SSCP (a polymerase proofreading method, allele specific PCR, and reading sequence data)

Applicants note that claim 5 is canceled, while its limitation is incorporated into amended claim 1. The distinction of claim 1 and Lorenz is noted above and discussed below, and by virtue of their dependency from claim 1, claims 6 and 7 are free of Lorenz.

Claim 8: **Lorenz** teaches that the risk genotype of the subject is indicative of increased likelihood of septic shock, *i.e.*, having a poor outcome from an inflammatory condition

Applicants note that by virtue of the amendment of parent claim 1, this claim refers to a different SNP and is free of Lorenz.

Claim 9: **Lorenz** teaches subjects that are critically ill, the presence of the **Lorenz** risk genotype is associated with septic, making the genotype predictive of severe CV dysfunction

Applicants note that by virtue of the amendment of parent claim 1, this claim refers to a different SNP/genotype and is free of Lorenz.

Claims 14-15: **Lorenz** teaches association of staphylococcal septic shock, an inflammatory condition associated with Gram-positive sepsis, septicemia, septic shock, SIRS, and fever. The inclusion criteria for SIRS are encompassed by this septic shock

Applicants note that claim 14 is canceled and by virtue of the amended of parent claim 1, claim 15 refers to an association of septic shock and a different SNP and is free of Lorenz.

Claim 40: **Lorenz** teaches that the inflammatory condition is associated with a gram positive (staphylococcal) infection)

Applicants note that by virtue of the amendment of parent claim 1, this claim refers to a different SNP/genotype associated with gram positive infection, and is therefore free of Lorenz. Claims dependent from claim 40 (claims 47-48) are similarly free of this reference.

Claims 42-45: **Lorenz** teaches that the SNP determination is performed on the nucleic acid of the sample by sequencing and polymerase proofreading method, allele specific PCR, and reading sequence data.

Applicants note that these claims are canceled.

Claim 46: **Lorenz** teaches that the SNP detected (*e.g.*, the risk genotype) is indicative of a gram positive infection

Applicants note that to the extend that this embodiment is incorporated into claim 40, the distinction of the SNP/genotype renders claim 40 free of Lorenz

Applicants Further Response to § 102 Rejection

As indicated in Applicants' brief comments above, **Lorenz** teaches a different polymorphism that is associated with staphylococcus septic shock. The notion expressed in the Action that position 201 as recited in prior claim 2 and polymorphisms LD therewith likely encompasses the polymorphism (Arg753Gln described in **Lorenz**. However, the amendments that limit claim 1 to position 201 of SEQ ID NO: 1 is adequate to distinguish over **Lorenz**. Therefore, this ground for rejection should be withdrawn.

XI. CONCLUSION

Applicants respectfully request entry of the foregoing claims as amended and their allowance. The scope of the current claims can no longer be considered to exceed the scope enabled by the specification or to lack adequate written description.

The Examiner is requested to phone the undersigned for any required clarifications, to discuss any remaining further impediments to allowance

Respectfully submitted,

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